

REMARKS

This paper is filed in response to the Final Office Action mailed June 24, 2009 (the “Office Action”). Claims 1 through 6, 10 through 18 and 22 were previously cancelled. Claims 7 and 19 are amended herein. For the reasons set forth below, Applicants submit that each of the pending claims is patentable and in condition for allowance. Therefore, reconsideration of the claims is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 7 through 9 and 19 through 21 are rejected under 35 U.S.C. § 112, First Paragraph. Applicants submit, however, that the as-filed specification of the present application fully enables each of claims 7 through 9 and 19 through 21, and Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 112, First Paragraph, be withdrawn.

It is asserted in the Office Action that “[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with [the pending] claims.” (*Office Action*, p.2). However, as is set forth in the Manual of Patent Examining Procedure (“the M.P.E.P.”), the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the art without undue experimentation. (See, *M.P.E.P.* § 2164.01, citing *United States v. Telecommunications, Inc.*, 857F.2d 778, 785, 8 USPQ2nd 1217, 1223 (Fed. Cir. 1988)). In this case, the teachings and experimental support provided by the specification specifically support the invention as it is recited in the pending claims, allowing one of ordinary skill in the art to not only appreciate the invention, but to make and use the invention as it is claimed.

The Office Action employs a two-part argument to assert that the specification is not enabling. First, it is argued that the specification provides only one *in vitro* working example, and second it is asserted that, in light of the lack of predictability in the art, the specification and the example provided therein would not allow one of ordinary skill to

practice the invention recited in the pending claims without undue experimentation. Applicants respectfully disagree with this line of reasoning, submit that the evidence used to support such arguments is not applicable and not relevant to the claimed invention, and provide documents in a simultaneously filed IDS that highlight the accuracy of the teachings provided in the as-filed specification of the present application.

At the time of filing, upon review of the teachings and guidance provided by the as-filed specification, one of ordinary skill in the art would have all the information needed to practice the claimed invention without undue experimentation. Claims 7 through 9 are directed to methods of "inhibiting migration of human microvascular endothelial cells (HMVECs) expressing a native Robo-4 receptor, the methods comprising exposing said HMVECs to a Slit ligand, wherein exposing said HMVECs to said Slit ligand inhibits migration of said HMVECs." Moreover, claims 19 through 21 are directed to methods for preventing angiogenesis requiring the migration of HMVECs, the method comprising, inhibiting migration of HMVECs expressing a native Robo-4 receptor, wherein inhibiting migration of said HMVECs comprises providing a Slit ligand and exposing said HMVECs to said Slit ligand such that migration of said HMVECs is inhibited. The teachings and guidance included in the specification of the present application, including the experimental evidence provided therein, specifically support such methods. In particular, it was stated in previous office actions that the specification is "enabling for a method of inhibiting migration of HMVECs" (*Office Action of February 19, 2009*, page 4), and in the current Office Action, it is still acknowledged that the experimental evidence provided in the specification establishes that "Slit2 inhibits the migration of HMVECs expressing Robo4 . . . in an *in vitro* cell migration assay . . ." (*Office Action*, p. 2 – p. 3). When the experimental results detailed in the specification are combined with the specific teachings provided by the specification, such as those found in paragraphs 42 through 45 and 50 through 52, one of ordinary skill in the art would be equipped with information sufficient to practice the full scope of the methods recited in the pending claims.

It is asserted in the Office Action that, given the unpredictability in the art, the specification would not equip one of ordinary skill with sufficient information to practice the invention in both *in vitro* and *in vivo* contexts. However, the enablement requirement does not dictate that the specification provide working examples describing every embodiment of a claimed invention, only that the specification as a whole allow one of ordinary skill to practice the invention without undue experimentation. (See, *M.P.E.P.* § 2164.02). Again, Applicants respectfully submit that the teachings of the specification, particularly in light of the experimental evidence provided therein, specifically enable the subject matter recited in the pending claims. Moreover, the evidence used to support the assertion that the art pertaining to the claimed subject matter is particularly unpredictable is either not applicable and not relevant.

Enablement must be assessed as of the time of filing. (See, *M.P.E.P.* § 2164.05(a)) “Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the **prior art**, and the level of skill in the art.” (See, *Id.*, emphasis added). “The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling . . .” (*Chiron Corp. v. Genentech, Inc.*, 363F3.d 1247, 1254, 70 USPQ2n 1321, 1325-26 (Fed. Cir. 2004)). Because publications dated after the filing date of an application generally cannot be used to show what was known at the time of filing, examiners, as a general rule, should not use post-filing date references to demonstrate an application is not enabling. (See, *M.P.E.P.* § 2164.05(a), citing *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402, 405-406 (CCPA 1976), and *In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977)). In this application, the Examiner has supported the assertions of unpredictability and the rejection of claims 7 through 9 and 19 through 21 under 35 U.S.C. § 112, First Paragraph, using references filed well after the effective filing date of the present application. Such references are simply not applicable to an assessment of enablement as of the time of filing, and Applicants, therefore, request that the rejection of the rejection under 35 U.S.C. § 112, First Paragraph, be withdrawn.

Though there is a limited exception that allows for consideration of post-filing date references in an analysis under 35 U.S.C. § 112, First Paragraph, such exception does not apply here. Specifically, a post-filing date reference may be used to assess enablement where that reference establishes that, after the filing date, it was not possible to carry out the claimed invention. (See, *M.P.E.P. § 2164.05(a)*, citing *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d, 1510, 1513-1514 (Fed. Cir. 1993)). However, that is simply not the case for the subject matter recited in pending claims 7 through 9 and 19 through 21. The Office Action cites two post-filing date references in support of the enablement rejection. However, neither of these references is relevant to the subject matter recited in the pending claims, and they certainly do not establish that it is not possible to carry out the claimed subject matter.

First, Wang (Cancer Cell. 2003 Jul;4(1):19-29) is cited in the Office Action. However, the teachings of Wang are directed to Robo1 receptors, not Robo4 or how the Robo4 receptor interacts with Slit peptides. Nothing in Wang establishes that it is not possible to carry out the subject matter recited in the pending claims. Moreover, the teachings in Wang run contrary to accepted literature regarding the function of Robo1 in non-neuronal cells. (See, *The neuronal repellant Slit inhibits leukocyte chemotaxis induced by chemotactic factors*, Wu JY, Feng L, Park HT, Havlioglu N, Wen L, Tang H, Bacon KB, Jiang Zh, Zhang Xc, Rao Y. *Nature*. 2001 410(6831):948-52)). The teachings of Wang, consequently, are not relevant to systems requiring the presence of Robo4, they are at odds with long-accepted teachings in the art, and they do not establish that it is not possible to carry out the claimed subject matter.

The second reference cited in the Office Action is Okada (Circ Res. 2007 Jun 22;100(12):1712-22). However, Okada also lacks guidance or results regarding the interactions of Robo4 with Slit ligands. The self-expressed goal of the work reported in Okada was to dissect the mechanism of cell-type specific expression of the Robo4 promoter. The work described in Okada was not concerned with the interaction of Slit ligands with Robo4, and nothing in Okada establishes that it is not possible to carry out the subject matter recited in the pending claims. Therefore, the teachings of Wang and Okada, whether considered alone or in combination, are not relevant to an enablement

analysis for the subject matter recited in pending claims 7 through 9 and 19 through 21. These references were not only published well after the filing date of the present application, but the teachings they provide are not relevant to the subject matter recited in the rejected claims. Again, Applicants respectfully request that the rejection of claims 7 through 9 and 19 through 21 under 35 U.S.C. § 112, First Paragraph, be withdrawn.

To the extent, the Examiner seeks to continue utilizing post-filing date references as support for rejections of the claims pending in this application, Applicants would like to draw the Examiner's attention to three articles that have been published or, in the case of the third article, are ready for print: 1) *Robo4 is a vascular-specific receptor that inhibits endothelial migration*, Park, KY, Morrison, CM, Sorenson, LK, Chien, CB, Wu JY, Li DY (2003); Dev Bio 261:251-26; 2) *Robo4 stabilizes the vasculature by inhibiting angiogenesis and endothelial hyperpermeability*, Jones C, London N, Park K, Chen H, Stockton R, Nishiya N, Ginsberg M, Zhang K, and Li DY (2008); Nature Medicine 14(4):448-53; and 3) *Slit2-Robo4 signaling promotes vascular stability by blocking Arf6 activity*, Jones CA, Nishiya N, London NR, Zhu W, Sorenson LK, Chan A, Lim CJ, Chen H, Zhang Q, Schultz PG, Hayallah AM, Thomas KR, Famulok M, Zhang K, Ginsberg MH, Li DY (2009, in press); Nature Cell Biology. Full copies of these articles are provided with an IDS filed simultaneously herewith. These articles illustrate that the teachings of the present application enable the subject matter recited in the pending claims, and the combined teachings provided by these three documents highlight that, it is, in fact, possible to carry out the subject matter recited in the pending claims in accordance with the teachings found in the present application.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 19 through 21 are rejected under 35 U.S.C. § 112, Second Paragraph. Applicants respectfully traverse this rejection.

It is asserted in the Office Action that claims 19 through 21 fail to particularly point out and distinctly claim the subject matter regarded to be the invention. Specifically, it is asserted that claim 19 is indefinite "because it lacks a process step which clearly relates back to the claim preamble . . ." (Office Action, p. 5). In order to

speed prosecution of this application, and without acquiescing to the assertion that previously presented claims 19 through 21 do not particularly point out and distinctly claim the subject matter regarded to be the invention, Applicants have amended claim 19 without prejudice or disclaimer such that the claim refers to a method of preventing angiogenesis requiring the migration of HMVECs, with a process step included in the method that requires inhibiting migration of HMVECs expressing a native Robo-4 receptor. Applicants respectfully submit that claim 19 and claims 20 and 21, which depend therefrom, now more clearly express a method comprising a process step relating back to the relevant preamble. Applicants, therefore, respectfully request withdrawal of the rejection of claims 19 through 21 under 35 U.S.C. § 112, Second Paragraph.

Claim Objections

Claim 7 is objected to due to a grammatical error. Applicants have amended claim 7 such that the noted error is corrected. Withdrawal of the objection to claim 7 is, therefore, respectfully requested.

Conclusion

In view of the foregoing, it is believed that all of the claims are patentable in their present form and a prompt notice of allowance for this application is respectfully requested. If the Examiner finds any remaining impediment to the prompt allowance of this application, please contact the undersigned attorney.

Respectfully submitted,

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